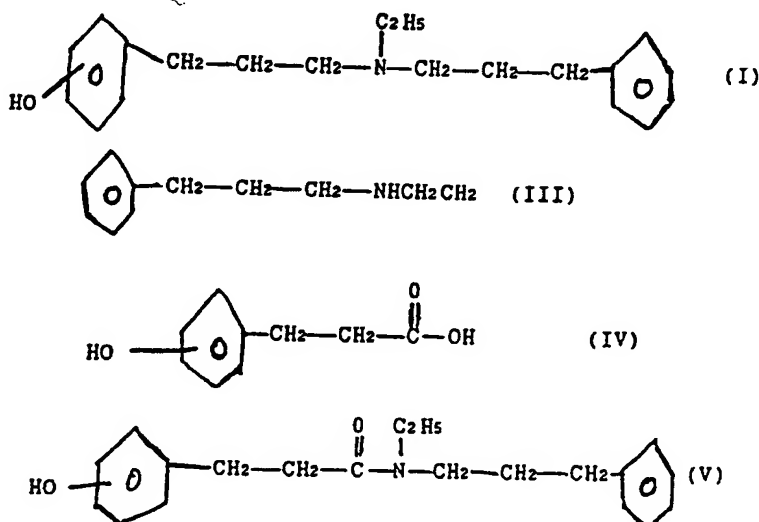




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<p>(21) International Application Number: PCT/GB91/01348</p> <p>(22) International Filing Date: 7 August 1991 (07.08.91)</p> <p>(30) Priority data: 9017390.7 8 August 1990 (08.08.90) GB</p> <p>(71) Applicant (for all designated States except US): NORGINE LIMITED [GB/GB]; New Road, Hengoed, Mid Glamorgan CF8 8SJ (GB).</p> <p>(72) Inventor; and</p> <p>(75) Inventor/Applicant (for US only) : HORGAN, William, J. [GB/GB]; 116-129 London Road, Headington, Oxford OX3 9BA (GB).</p> <p>(74) Agent: KING, James, Bertram; 11rbert J.W. Wildbore, 73 Farringdon Road, London EC1M 3JB (GB).</p>	<p>(81) Designated States: AT, AT (European patent), AU, BB, BE (European patent), BF (OAPI patent), BG, BJ (OAPI patent), BR, CA, CF (OAPI patent), CG (OAPI patent), CH, CH (European patent), CI (OAPI patent), CM (OAPI patent), CS, DE, DE (European patent), DK, DK (European patent), ES, ES (European patent), FI, FR (European patent), GA (OAPI patent), GB, GB (European patent), GN (OAPI patent), GR (European patent), HU, IT (European patent), JP, KP, KR, LK, LU, LU (European patent), MC, MG, ML (OAPI patent), MN, MR (OAPI patent), MW, NL, NL (European patent), NO, PL, RO, SD, SE, SE (European patent), SN + (OAPI patent), SU, TD (OAPI patent), TG (OAPI patent), US.</p> <p>Published <i>With international search report.</i></p>	

(54) Title: **PROPYLAMINE DERIVATIVES**

(57) Abstract

Novel propylamine derivatives having general formula (I) and quaternary bases thereof. Such compounds exhibit antispasmodic activity. Compounds (I) may be prepared by coupling a compound having formula (III) with a compound having general formula (IV) to produce a compound having general formula (V) and reducing the compound (V) to the amine having general formula (I). The coupling agent may be dicyclohexyl carbodimide and the reducing agent may be lithium aluminium hydride.

+ DESIGNATIONS OF "SU"

It is not yet known for which States of the former Soviet Union any designation of the Soviet Union has effect.

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TITLE

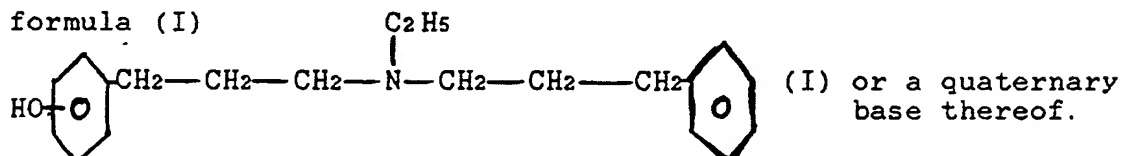
Propylamine Derivatives

5 Certain nitrogen containing materials, sometimes in the form of amines or quaternary bases, are known to possess antispasmodic activity.

 The present invention provides a propylamine derivative (I) (hereinafter defined) which we have shown
10 to possess significant antispasmodic properties.

 The compound (I) is probably best used in one of its salt forms, e.g. its hydrochloride, as this increases water solubility and may improve its bioavailability.

 According to one aspect of the invention there is
15 provided a propylamine derivative having the general



 An especially useful compound within the general formula
20 (I) is compound (II) which is N-ethyl, N-(3-phenyl propyl), 3-(4-hydroxyphenyl)-propylamine, i.e. the para hydroxy compound.

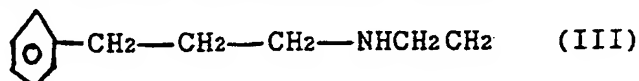
 The said propylamine derivative (I) or (II) may be in the form of a pharmaceutically acceptable inorganic salt, e.g. the hydrochloride thereof, or organic salt,
25 e.g. the citrate.

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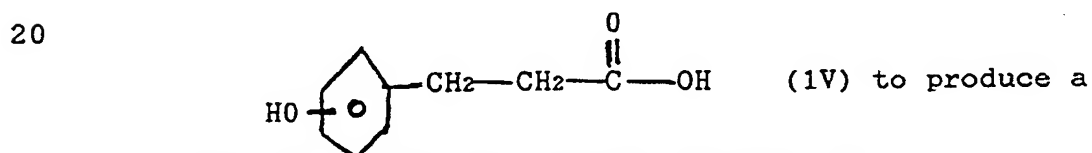
According to another aspect of the invention there is provided the use of the compound (I) or a quaternary base thereof, or a pharmaceutically acceptable salt thereof as an antispasmodic agent.

5 According to a further aspect of the invention there is provided a composition comprising a compound (I) or a quaternary base thereof or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier therefor. Such a composition may be in the form of
10 tablets, capsules, microspheres, liquid, semisolid or suppository dosage. Such a composition may be administered by oral, intravenous, intramuscular, topical or rectal route.

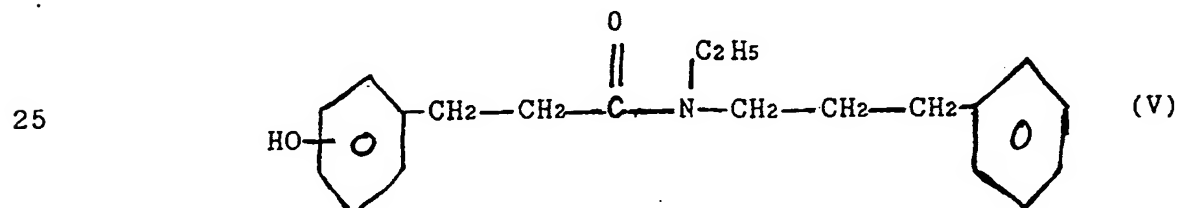
According to a still further aspect of the invention
15 there is provided a method for the production of compound (I) comprising coupling, using a coupling agent, a compound having the formula (III)



with a compound having the general formula (IV)



compound having the general formula (V)



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and reducing, using a reducing agent, the compound (V) to the amine having the general formula (I) as defined above.

Preferably the said coupling agent is dicyclohexyl carbodimide, preferably in methylene chloride, and preferably the said reduction is achieved by the use of lithium aluminium hydride as reducing agent, preferably in diethyl ether.

Preparative Example


Preparation of N-ethyl, N-(3-phenyl propyl),
3-(4-hydroxyphenyl)-propylamine (II)

The synthesis commences with 3-(phenyl) propionic acid (dihydrocinnamic acid) (a) having the formula



corresponding acid chloride having the formula


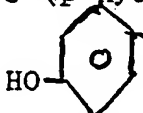


Treatment of this acid chloride (VII) with a large excess of anhydrous ethylamine gives a white crystalline amide having the formula (VIII)  in good yield. Reduction of the said amide with lithium aluminium hydride worked well in diethyl ether (c) (but not tetrahydrofuran) to give a thick yellow brown oil which was slower on TLC (thin layer chromatography). The distinctive pair of H² protons were observed at 1.8 ppm in the proton nuclear magnetic (¹H NMR) spectrum. The

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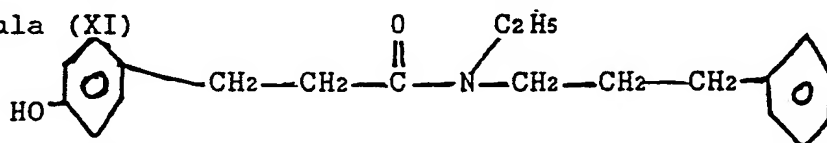
product could be extracted into aqueous acid and gave a positive colour test with benzyl p-nitrophenyl formate due to the liberation of p-nitrophenol (yellow). Both of these are positive tests for the presence of an amine group.

The resultant amine which has the formula

 $\text{CH}_2\text{—CH}_2\text{—CH}_2\text{—NH—CH}_2\text{—CH}_3$ (IX) was successfully coupled with 3-(p-hydroxyphenyl) propionic acid having the formula  $\text{CH}_2\text{—CH}_2\text{—COOH}$ (X) using

dicyclohexyl carbodimide (DCC) in methylene chloride. The major part of the by-product, dicyclohexyl urea (DCU), was removed by filtration of the crude reaction mixture and the rest precipitated from a concentrated solution after aqueous work-up. The tertiary amide having the

formula (XI)



gave the characteristic AB splitting pattern of the p-hydroxyalkyl moiety in the aromatic region of the ^1H NMR spectrum.

The amide (XI) was reduced using lithium aluminium hydride in diethyl ether, where the ether to amide ratio was in the range 20:1 to 30:1, (a b c) to give the required product N-ethyl, N-(3-phenyl propyl), 3-(4-hydroxyphenyl)-propylamine (II).

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EXPERIMENTALN-ethyl 3-phenyl propylamide (VIII)

Prepared according to literature procedure. (b) ¹H NMR
7.6 (5H, s, aromatics); 3.2 (2H, m, 2H²); 2.9 (2H, m
5 2H⁴); 2.4 (2H, m, 2H¹); 1.0 (3H, t, 7hz, 3H⁵).

N-ethyl 3-phenylpropylamine (IX)

Lithium aluminium hydride (5.78 g, 152 mmoles) was
dissolved in dry diethyl ether (250 ml) in a 3 neck 1L
flask fitted with a dropping funnel, reflux condenser,
10 stopper and magnetic stirrer bar. All exits were closed
with drying towers. The solution was brought to reflux
and the heat removed. The amide (VIII) (16 g, 90
mmoles) dissolved in dry diethyl ether (250 ml) was added
dropwise over 30 minutes with vigorous stirring. The
15 solution was then refluxed for 36 hours. Water (700 ml)
was added cautiously; the gummy gel was filtered and the
filtrate extracted with ether (5 x 350 ml). The
combined organic extracts were dried over magnesium
sulphate, filtered and evaporated to give a yellow oil
20 (14.5 g, 100%).

TLC Starting material Rf 0.46

Product Rf 0.2

Silica gel plates, eluant 98% chloroform, 2% methanol/¹H
NMR (CDCl₃) 7.2 ppm (5H, m, aromatics); 2.65 (6H, m, 2H¹,
25 2H³, 2H⁴); 1.8 (2H, m, 2H²); 1.1 (3H, t, 7hz, 3H⁵).

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N-ethyl, N-(3-phenylpropyl), 3-(4-hydroxyphenyl)-
propylamide (XI)

The acid (X) (50 g, 0.3 mole) and DCC (32 g, 0.16 mole) were suspended in methylene chloride (200 ml). The amine (IX) (16 g, 0.1 mole) was added dropwise from a pressure equalised dropping funnel. A mild exotherm was produced. After two hours stirring the reaction mixture was filtered and the filtrate poured into saturated sodium bicarbonate (300 ml) which was extracted with methylene chloride (5 x 200 ml). The collected extracts were dried with sodium sulphate and evaporated to give an orange oil (51.68 g). The precipitate which was filtered off was shown to consist entirely of DCU by ^1H NMR. The oil was dissolved in hot benzene, additional DCU precipitated and was filtered off (yield 30 g, 93%). ^1H NMR (CDCl_3) 7.5-6.9 ppm (10H, m, aromatics, OH); 3.5-2.2 (10H, m, 2H^1 , 2H^2 , 2H^4 , 2H^6 , 2H^7); 2-1.5 (2H, m, 2H^5); 1.1 (3H, t, 7hz, 3H^8).

N-ethyl, N-(3-phenylpropyl), 3-(4-hydroxyphenyl)-
propylamine (II).

Lithium aluminium hydride (20 g, 52 mmoles) was dissolved in dry diethyl ether (1L, CaH_2 dried) in a 10L three neck flask fitted with a reflux condenser, dropping funnel, stopper and a magnetic stirrer. All exits were closed with drying tubes. The amide (XI) 40 g, 12.8

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mmoles) in dry diethyl ether (1L) was added dropwise to a gently refluxing solution, over 1 hour. The condenser was transferred to the dropping funnel and the funnel was washed clean by reflux. The condenser was then returned to its former position and reflux maintained for 4 hours. Addition of water (5 ml) and magnesium sulphate heptahydrate (100 g) gave a solid which which was filtered and washed with water (2L) and diethyl ether in alternate small portions. Separation of the phases and extraction of the aqueous phase with ether (8 x 300 ml) followed by magnesium sulphate drying, filtration and evaporation gave a yellow oil, which was further dried by azeotrope with benzene. The aqueous phases had a pH of 11 which is a little too high for a phenol extraction. Accordingly, hydrochloric acid was added to pH5 and this was neutralised with sodium bicarbonate to pH8. However, further extraction only gave traces of 3-(4-hydroxyphenyl) propionic acid (confirmed by ¹H NMR).

TLC Product R_f 0.2 eluant 95% chloroform, 5% methanol ¹H NMR (CDCl₃) 7.4 ppm (5H, m, phenyl); 7.2 (2H, 8hz, aromatics, part of AB pair); 6.2 (1H, brs, OH); 2.5 (10H, 2H¹, 2H³, 2H⁴, 2H⁶, 2H⁷); 1.8 (4H, m, 2H², 2H⁵); 1.0 (3H, t, 7hz, 3H⁸).

Antispasmodic Activity

Antispasmodic activity was determined using standard

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methodology. (d)

Guinea-pig ileum muscle was suspended in a gut bath, in oxygenated Tyrode's solution at 37°. Doses of acetylcholine were added to the gut bath fluid, the contraction recorded, and the bath washed out with fresh Tyrode's solution. This was carried out repeatedly to establish a dose of acetylcholine to cause a sub-maximal response. This dose of acetylcholine was used repeatedly, on a 2 minute cycle to establish steady responses. Doses of antispasmodic were then added 30 seconds before the acetylcholine dose to establish the magnitude of reduction of the acetylcholine contraction.

Using atropine sulphate as a standard, N-ethyl, N-(3-phenyl propyl) 3-(4-hydroxyphenyl)-propylamine (II) in the hydrochloride form was shown to have an antispasmodic activity approximately 25 times less than the standard (1.5 ng of the said amine hydrochloride was equivalent to 0.06 ng of atropine sulphate.)

Literature references (a) - (d) are listed below.

- 9 -

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- (a) T. Hudlicky, Reductions in Organic Chemistry, Ellis
Horwood, Chichester, 1984.
- 5 (b) A.C. Cope and E Ciganek, Organic Synthesis, 1960,
39, 19.
- (c) V.M. Micovic and M.L. Mihailovic, J. Org. Chem.,
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- 10 (d) Pharmacological Experiments on Isolated
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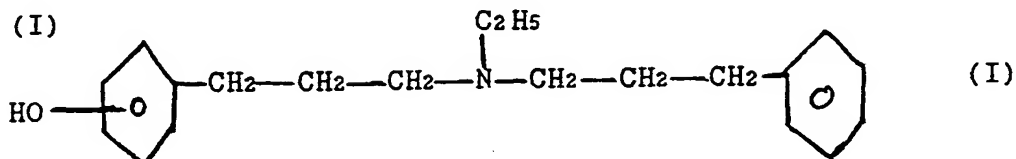
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CLAIMS

1. A propylamine derivative having the general formula



or a quaternary base thereof.

2. N-ethyl, N- (3- phenyl propyl), 3- (4-hydroxyphenyl)

- propylamine or a quaternary base thereof.

3. A compound as defined in Claim 1 or Claim 2 which is in the form of a pharmaceutically acceptable inorganic salt.

4. A compound according to Claim 3 which is in the form of a hydrochloride thereof.

5. A compound as defined in Claim 1 or Claim 2 which is in the form of a pharmaceutically acceptable organic salt.

6. A compound according to Claim 5 which is in the form of a citrate thereof.

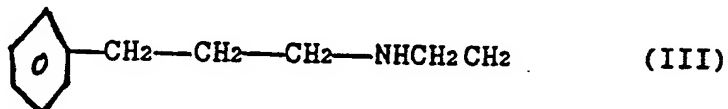
- 11 -

7. The use of a compound as defined in any one of Claims 1 to 6 as an antispasmodic agent.

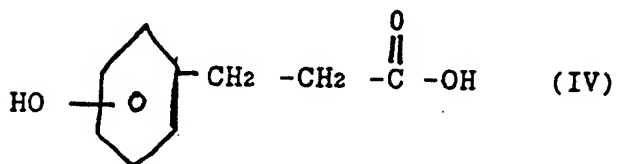
8. A composition comprising a compound as defined in any one of Claims 1 to 6 and a pharmaceutically acceptable carrier therefor.

9. A composition according to Claim 8 which is in the form of tablets, capsules, microspheres, liquid, semisolid or suppository dosage.

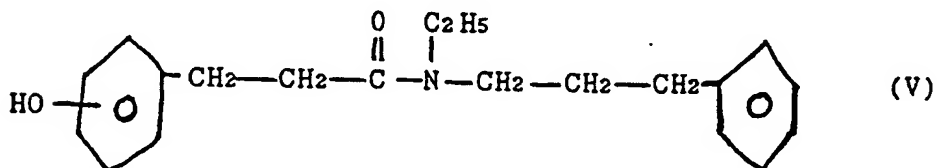
10. A method for the production of a compound (I) comprising coupling, using a coupling agent, a compound having the formula (III)



with a compound having the general formula (IV)



to produce a compound having the general formula (V)



and reducing, using a reducing agent, the compound (V)

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to the amine having the general formula (I).

11. Method according to Claim 10, wherein the said coupling agent is dicyclohexyl carbodimide.

5

12. Method according to Claim 10 or Claim 11, wherein said reduction is achieved by the use of lithium aluminium hydride as reducing agent.

10

13. A propylamine derivative as claimed in any one of Claims 1 to 6 for use as an active pharmaceutical substance.

15

14. A propylamine derivative as claimed in any one of Claims 1 to 6 for use as an antispasmodic agent.

15. A method according to Claim 10 substantially as herein described and exemplified.

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16. A compound as defined in any one of Claims 1 to 6 substantially as herein described and exemplified.

17. A composition according to Claim 8 substantially as herein described and exemplified.

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SUBSTITUTE SHEET

INTERNATIONAL SEARCH REPORT

International Application

PCT/GB 91/01348

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)⁶

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07C215/54; A61K31/135

II. FIELDS SEARCHEDMinimum Documentation Searched⁷

Classification System	Classification Symbols
Int.Cl. 5	C07C

Documentation Searched other than Minimum Documentation
to the Extent that such Documents are Included in the Fields Searched⁸**III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹**

Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claims No. ¹³
A	CHEMICAL ABSTRACTS, vol. 78, no. 11, 19 March 1973, Columbus, Ohio, US; abstract no. 67072D, IRESON, J.D: 'Effects of Alverine citrate on smooth muscle' page 38 ; column 1 ; see abstract & PHARMACOLOGICAL RESEARCH COMMUNICATIONS vol. 4, no. 3, 1972, pages 191 - 194; & CHEMICAL SUBSTANCE INDEX, PAGE 5419CS 'Benzenep ropanamine, N-ethyl-N-(3-phenylpropyl)-'	1-17

¹⁰ Special categories of cited documents:^{"A"} document defining the general state of the art which is not considered to be of particular relevance^{"E"} earlier document but published on or after the international filing date^{"L"} document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)^{"O"} document referring to an oral disclosure, use, exhibition or other means^{"P"} document published prior to the international filing date but later than the priority date claimed^{"T"} later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention^{"X"} document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step^{"Y"} document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.^{"A"} document member of the same patent family**IV. CERTIFICATION**

Date of the Actual Completion of the International Search

08 NOVEMBER 1991

Date of Mailing of this International Search Report

02.12.91

International Searching Authority

EUROPEAN PATENT OFFICE

Signature of Authorized Officer

i.m.helps

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GB-A-	115410
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